ICF Consulting Review of NPB AEL Recommendation Proposed by Doull and Rozman

Introduction

Acceptable exposure limits (AELs) for occupational exposures are intended to represent the upper bound of chemical exposure that would be protective of worker health. EPA has received an occupational exposure limit recommendation for n-propyl bromide (NPB), also referred to as 1-bromopropane or 1-propyl bromide, that was developed by Doull and Rozman (2001). In addition to the AEL recommendation, the Doull and Rozman (2001) report included information regarding the chemical and physical properties of NPB, an overview of the relevant toxicity studies, and references to studies conducted with structurally analogous chemicals, such as 2-bromopropane (2-BP). This document is a response to the conclusions provided in the Doull and Rozman (2001) report, and in particular to the derivation of an AEL for NPB.

Findings

In general, the Doull and Rozman (2001) report was clearly written and contained accurate information regarding the toxicity studies conducted with NPB. However, some of the conclusions drawn were not sufficiently supported by the data. For example, the Doull and Rozman (2001) report concludes that exposures to NPB at doses comparable to those used in the ethyl bromide carcinogenicity assay would not result in carcinogenic effects for the following reasons: 1) the lack of positive genotoxicity data with NPB at non-cytotoxic doses, 2) the relative genotoxicity ranking of NPB and structurally similar chemicals, and 3) limited evidence of carcinogenicity in bioassays conducted with structurally analogous chemicals (i.e., ethyl bromide and methyl bromide).[1] This assertion would hold true if NPB and ethyl or methyl bromide were to have the same mode of action for the potential induction of carcinogenic effects, and if the dose-response relationship for these carcinogenic effects were comparable. However, if NPB were to act via a mode of action different from that of ethyl or methyl bromide, then tumor formation could possibly result. Nevertheless, given that there is no evidence that exposures to NPB induce cancer in humans or animals, speculation regarding the dose at which a negative result might be expected is not warranted.

Selection of Critical Endpoints

Doull and Rozman (2001) concluded that the results of the various animal toxicity studies conducted with NPB indicate that nervous system effects are the most sensitive endpoint. This assertion is based on a lowest observed adverse effect level (LOAEL) of 200 ppm (the lowest concentration tested) for decreased hind limb grip strength in mice reported by Ichihara et al.

[1]The authors reported that the only positive finding in the bioassays conducted with ethyl bromide and methyl bromide was a significant increase in the incidence of uterine cancer in mice exposed to 400 ppm.

(1999). Confidence in the data presented by Ichihara et al. (1999), however, is low for a number of reasons. Specifically, these results have been presented in a series of very brief abstracts that were presented at the Annual Meeting of Japan Society for Occupational Health. Based on a previous review of these abstracts performed by ICF Consulting, it is unclear if comparisons were made to concurrent controls. There were also discrepancies in the number of animals used. In addition, there was no indication that the studies complied with Good Laboratory Practice (GLP) guidelines and that appropriate quality assurance/quality control reviews were made. Although these issues are not apparent in the subsequent published article by Ichihara et al. (2000), it appears that at least some of the data reported in Ichihara et al. (2000) were also presented in the unpublished abstracts.

In a study conducted by ClinTrials (1997), decreases in grip strength were not observed in rats exposed to up to 600 ppm NPB for 6 hours/day, 5 days/week for 13 weeks (ClinTrials 1997). In fact there were no consistent treatment-related changes reported in the treated rat following 4, 8, or 13 weeks of exposure in any parameter evaluated in a full functional observational battery. These data argue against the selection of nervous system effects as the most sensitive endpoint following exposure to NPB.

Doull and Rozman (2001) considered reproductive effects to be the second most sensitive set of endpoints, with a no observed adverse effect level (NOAEL) of 100 ppm and a LOAEL of 250 ppm based on increased estrous cycle lengths (F_1 females) and reduced prostate and epididymal weights (F_0 males) (WIL Research 2000). In light of the questions surrounding the CNS data reported by Ichihara and colleagues, however, ICF considers the data presented in the study by WIL Research (2000) to be more appropriate for use as the basis for an AEL. Based on a review of the animal toxicity data, ICF has concluded that the weight of the evidence indicates that the effects on the reproductive system (i.e., decreases in sperm motility) and the liver (i.e., centrilobular vacuolation) are in fact the most sensitive endpoints (ClinTrials 1997; WIL Research 2000).

Epidemiological Data

Reviews of several epidemiological studies were also included in the report by Doull and Rozman (2001). Epidemiological studies may provide useful information regarding the potential toxic effects of a chemical in humans and may be used to establish a dose-response for a particular effect, provided that 1) exposures are well characterized, 2) the sample size is large enough to allow for the detection of subtle effects, and 3) comparisons to unexposed control populations are made. All but one of these studies described in Doull and Rozman (2001) describe effects observed in workers exposed to 2-bromopropane (Kim et al. 1996, 1999; Park et al. 1997; Ichihara et al. 1999).

The data from NIOSH (1999), the only study within the Doull and Rozman (2001) report that involves NPB, should be interpreted with caution. In the NIOSH study, only 43 of 70 workers at Custom Products (Mooresville, NC), a seat cushion manufacturing plant, were evaluated for NPB exposure. These individuals were grouped into exposure categories of low, medium, or high, with mean NPB exposures of 117 ppm, 170 ppm, and 197 ppm, respectively, based on the results of a NIOSH exposure survey. No control group was used. A questionnaire was used to determine the frequency of symptoms including headache (at least once per week), feeling drunk in the absence of alcohol consumption, abnormal fatigue, and problems concentrating. In addition, questions regarding fertility and reproductive outcomes were also included in the questionnaire. Blood samples were collected and complete blood counts (CBCs) were performed.

Doull and Rozman (2001) based their no observed effect level (NOEL) on worker headache incidence. In the NIOSH report, 43 percent (3/7), 44 percent (8/18) and 61 percent (11/18) in the low, medium, and high exposure groups, respectively, reported having a headache at least once per week. Based on these results, Doull and Rozman (2001) concluded that the NOEL for headache was 170 ppm (with a LOEL of 197 ppm), the mean exposure concentration for individuals assigned to the medium exposure category. As discussed above, however, these results were obtained using a very small sample size, with no comparisons to an unexposed control group. Without comparisons to a control group, it is difficult to determine at what exposure concentration the headaches were related to NPB exposure. In fact, in a subsequent publication of the same study (NIOSH, 2002), NIOSH authors concluded that no statistically significant dose response trend could be identified from these data. Therefore, Doull and Rozman's conclusion that 170 ppm is the NOEL for NPB-induced headaches is inappropriate and these data should not be used to inform the AEL.

In their derivation of an AEL for NPB, Doull and Rozman (2001) indicated that due to the steepness of the dose-response relationship for neurological effects, a safety factor of 2 would protect most of the workers and a factor of 3 would provide a larger margin of safety. Due to the small sample size and the low sensitivity of the questionnaires, ICF believes that a larger safety factor would be required to ensure adequate protection of worker health. ICF agrees that workers should be protected from potential exposure-related headaches. However, an AEL of 60 to 90 ppm is not sufficiently low to ensure workers will be protected.

In their report, Doull and Rozman (2001) concluded that reproductive toxicity did not occur in the workers exposed to up to 190 ppm NPB based on the results of the NIOSH (1999) report. The authors of the NIOSH report noted that 3 workers (2 male and 1 female) that had been exposed to between 110 and 157 ppm NPB reported difficulty in having a child. However, as noted by the author of the NIOSH (1999) report, due to the limited sample size and the nature of the questions, there may have been substantial limitations in the ability of the NIOSH (1999) survey to detect reproductive or fertility problems. In addition, in a subsequent analysis and publication, NIOSH further evaluated these same data (2002). In this final report the authors state that for each of the symptoms evaluated in the medical survey, air concentrations of nPB were not statistically different between those employees reporting the symptom compared to those that did not report the symptom. Consequently, ICF considered the NIOSH (1999) data insufficient to draw firm conclusions regarding the potential reproductive toxicity of NPB in humans. Therefore, Doull and Rozman's conclusion that humans are as sensitive as or less sensitive than rats to reproductive toxicity as a result of exposure to NPB is not warranted.

Conclusions

The toxicity of NPB in rats has been well characterized and the database consists of a well conducted subchronic (90-day) toxicity study and a two-generation reproductive toxicity study in rats. Data from human populations are limited, and no dose response relationship could be identified. Ideally, when establishing an exposure guideline, such as an occupational exposure limit, data from humans exposed to the chemical of interest would be preferred as the basis for the guideline. However, the existence of human data does not always mean that these data are the best for the derivation of an AEL. Rather, all of the data, both human and animal, should be carefully evaluated in order to select the critical study and the critical effect.

In the document prepared by Doull and Rozman (2001), the results obtained from a questionnaire that had been administered to 43 workers exposed to NPB (NIOSH 1999) were used as the basis for derivation of an AEL. The critical effect was considered to be the frequency with which these individuals reported headaches occurring at least once per week. ICF agrees that one possible symptom resulting from exposures to solvents, such as NPB, is the occurrence of headaches. However, the data provided in the NIOSH Health Hazard Evaluation reports were inadequate to characterize the dose-response for exposure to NPB with regard to the occurrence of headaches and there was no control population for comparison. Effects on the reproductive system in both males and females are more consistently noted in the published literature for NPB; moreover, these effects are observed at lower concentrations than those typically reported for CNS effects. As noted by NIOSH, the data in their report were limited in their ability to detect reproductive problems in humans. Further, the NIOSH data contain self-reported symptoms with no corresponding controls; therefore, the data are potentially biased.

Therefore, ICF believes that data other than the NIOSH medical survey at Custom Products should be used to develop an AEL for NPB. The available data do not support the AEL of 60-90 for NPB that Doull and Rozman recommend.

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